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Genetic Syndromes as a Cause of Obesity in Saudi Paediatric Population - A Narrative Review

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Abstract Childhood obesity remains one of the most significant health issues worldwide, affecting over 340 million individuals around the world. Research indicates that childhood obesity is prevalent in at least 1.8 per 1000 live births in Saudi Arabia. The genetic disposition greatly influences obesity in these nations as can be inferred from twin studies and identification of rare monogenic obesity types. Obesity is a multifaceted characteristic arising from an intricate interplay of contributing factors, including genetic and environmental influences, that collectively elevate the risk of disease. Inactive lifestyles and calorie-rich diets are significant environmental contributors to the obesity epidemic. The genetics of childhood obesity differs in particular ways from the genetics of adult obesity. Adult obesity and its associated disorders have been known to be correlated to childhood BMI. Among the childhood obesity syndromes, Prader Willi and Bardet Biedl syndromes are among the most well-known. Thus, this review discusses about the highlights of obesity related genetic syndromes and their prevalence in the population of Saudi Arabia.

Key Words Genetic Syndromes, Obesity, Saudi Arabia, Childhood obesity, Children

INTRODUCTION

With over 340 million cases documented worldwide in 2017, childhood obesity can be considered a major global health concern [1]. Sedentary lifestyle and heightened intake of fat-rich foods linked to enhanced living conditions has led to the rise of childhood obesity in Arab countries significantly [2]. Research indicates that childhood obesity is prevalent in at least 1.8 per 1000 live births in Saudi Arabia [3,4]. The genetic disposition greatly influences obesity in these nations as can be inferred from twin studies and identification of rare monogenic obesity types [5,6]. Currently, it is considered that obesity is a complicated and multifaceted condition that is produced by a number of interactions that involve numerous elements. These interactions include multiple factors, such as metabolic, environmental, behavioural, cultural, economic, sociodemographic and genetic aspects [7].

Obesity is a multifaceted condition arising from the interaction of contributory components, comprising of genomic and environmental elements, which collectively contribute to the development of the disease [8]. High-calorie consumption and sedentary lifestyle are substantial environmental factors that influence the obesity epidemic. The genetic factors influencing childhood obesity are distinct from those affecting adult obesity [9,10]. The combined effects environment and genes undergo a substantial transformation from birth to maturity and are influenced by sex-specific factors. The progression of BMI is especially vital in infancy stages from 0.5 to 1.5 years and from 5 to 6. During this phase, the trajectory of BMI is established [11]. Later, the dynamic function of differential genetic expression of obesity due to age gets further complicated by sex-specific genetic effects [9].

Adult adiposity and its associated problems have been linked with childhood BMI [12,13]. The Middle East region possesses the biggest dietary energy surplus among emerging nations, which is linked with an alarming rise in risk factors for noncommunicable diseases, especially obesity [14]. A systematic review of 76 variants identified 76 variations inside or next to 49 genes that are significantly related with obesity, based on a cohort of 15,488 Arab cases and 9,760 controls. 19 of the 76 variants were identified as linked with obesity in Arab populations, but not in non-Arab groups, while two were characterized as exclusive to Arabs [15]. Similarly, 13 findings from a recent systematic review

conducted in 2022 identified 30 more cases of severe early-onset of obesity. 14 variants in five genes (LEP, LEPR, POMC, MC4R and CPE) were identified during the study. These pathogenic, homozygous variants were found in members of consanguineous families [16].

Genetic variants of obesity, although displaying a range of clinical characteristics, have traditionally been divided in three specific subtypes: Mendelian (monogenic) syndromic obesity, Mendelian non-syndromic obesity and polygenic obesity [17]. Pleiotropic syndromes, often known as syndromic variants of Mendelian obesity, are comparatively uncommon in the general population. Syndromic obesity is defined as obesity with particular characteristics, such as dysmorphic traits, congenital defects and intellectual disability that affects certain organ systems and Prader-Willi and Bardet-Biedl remain two of the most recognized obesity syndromes [18,19]. Access to accurate regional information, including epigenetic trends and credible national genetic data is crucial for a region-wise initiative to tackle the mounting problem of genetic origins of childhood obesity. Thus, our review discusses about the highlights of genetic syndromes related to obesity and their prevalence on Saudi population.

Genetic Syndromes and Obesity

A few genetic syndromes that are associated with obesity are as follows:

Monogenic Obesity Syndromes

Bardet-Biedl Syndrome (BBS)

Georges Bardet and Arthur Biedl identified BBS as a rare autosomal recessive disorder. It results in defects in multiple organ systems throughout the body and therefore, multisystemic in nature. This pleiotropic ciliopathy is defined by 6 primary characteristics, which include postaxial polydactyly, truncal obesity, hypogenitalism, retinal degeneration, renal abnormalities and mental disability, as evidenced by their prevalence in the patient population [20,21]. Obesity ranks as the second most common trait of BBS, impacting 72-92% of individuals diagnosed with the condition. The BMI for females and males have been reported to be 31.5 and 36.6 mg/m2, respectively [22]. It typically shows itself in childhood and tends to grow more severe with age. The physiological approaches show that obesity can originate from either centre or the periphery. At the molecular level, it has been found that the overexpression of Tumor Necrosis Factor (TNF) α in the adipose and muscle tissues significantly contributes to insulin resistance in the context of immune response-mediated obesity. The vital contribution of the inflammatory immune response in obesity is highlighted by the role of TNFα as a primary mediator of this response [24].

Alström Syndrome (ALMS)

ALMS, an extremely rare genetic disorder, occurs in approximately one in a million individuals, due to pathogenic variations in the ALMS1 gene which is located on chromosome 2p13, comprising of 23 exons and encoding a predicted protein weighing 461.2 kDa with 4169 amino acids [25]. Detecting ALMS proves challenging due to presence certain characteristics at birth while others manifest as the child matures. Significant variation exists both intra- and inter-familially. Children with ALMS typically exhibit prominent phenotypes such as sensorineural hearing loss, infant cone-rod retinal dystrophy that can lead to insulin resistance, obesity and juvenile blindness. Common findings include infantile transient cardiomyopathy, deafness, type 2 diabetes mellitus (T2DM), infantile transient cardiomyopathy, systemic fibrosis, early childhood obesity with hyperphagia, progressive renal or liver dysfunction and insulin resistance. The transportation of glucose is regulated by ALMS1 via the actin cytoskeleton, that becomes crucial for insulin-stimulated GLUT4 transport [26]. Abosabie et al in 2024 conducted a systematic review in 2024 and found that ALMS1 gene's molecular genetic assessment is essential for confirming the diagnosis, offering conclusive clarity within the complex clinical presentation [27].

Cohen Syndrome

The detection of Cohen syndrome' is done through medical observations or by detecting presence of pathogenic allelic variations in VPS13B (also known as COH1) through molecular genetic testing when clinical manifestations are ambiguous [28]. This is an autosomal recessive genetic disorder caused by a defective gene situated on chromosome 8 at 8q22-q23. Cohen syndrome is marked by the development of truncal obesity and a failure to thrive during childhood in more than 80% of affected adolescents [29]. The mean age at which obesity begins is 11.3 years. Reports indicate a swift transformation occurring within a span of 4-6 months, despite the absence of notable alterations in appetite, dietary consumption, or physical activity [30].

Carpenter Syndrome (CRPTS)

CRPTS is an autosomal recessive disorder identified primarily by and craniosynostosis and polysyndactyly of the feet and hand. Additional characteristics that have been reported include cryptorchidism, congenital heart disease and obesity [31]. CRPT, present in around 1 in 1 million births, is marked by obesity, polydactyly, heart abnormalities and craniosynostosis [32,33]. CRPTS is classified into 2 distinct types. Carpenter syndrome-1 (CRPT1) is caused by homozygous mutations in the RAB23 gene [34]. The Human Gene Mutation Database (HGMD) indicates that individuals with CRPT1 have been recorded to have only 17 pathogenic RAB23 variants [35]. Carpenter Syndrome-2 (CRPT2) is primarily caused due to mutations in the MEGF8 gene [36].

Albright's Hereditary Osteodystrophy (AHO)

Initial findings on AHO reported a child with a rounded facial structure, abbreviated metacarpals and metatarsals, along with

multiple regions of soft tissue ossification and a short, stocky physique [37]. 50-65% of individuals with AHO, even with normal or low birth weights were reported to have generalized obesity. Although the exact causes of obesity remain unknown, multiple potential mechanisms may be at play [38]. G-proteins transduce the melanocortin receptor (MC4R), which is identical to many other G-protein-coupled seven transmembrane receptors which transmit anorexigenic signals from hormones and other neurotransmitters. Mutations in this receptor were among the most common causes of genetic obesity. This lack of anorexigenic signals, particularly those involving MC4R, is believed to lead to hyperphagia; nonetheless, this occurrence is yet to be fully investigated in obese AHO individuals [39].

Rubinstein-Taybi Syndrome(RSTS)

RSTS is a multisystem disorder marked by distinct physical, cognitive and behavioural features. It is named after US paediatrician Jack Rubinstein and Iranian radiologist Hooshang Taybi, who reported on seven affected infants in 1963 [40]. It potentially arises from variations in 2 genes that regulate transcription via chromatin remodelling. This disorder is marked by presence of dysmorphic features, such as broad toes, broad thumbs and clinodactyly. In certain instances, obesity may also present itself during childhood and adolescence. Approximately 90% of individuals with RSTS attain adulthood despite the need for costly and specialised clinical treatment. After the patients reach adulthood, RSTS is marked by mental and behavioural health disorders (83%), insomnia (62%) and gastrointestinal issues like constipation being the most prevalent (73%) [41]. In the 1990s, the molecular basis of RSTS was first reported when deletions in 16p13 region of chromosome 16 were observed in affected patients, which subsequently led to identification of pathogenic variations in CREBBP gene [42]. RSTS can be categorized into two main variations, both showing autosomal dominance. RSTS type 1 is caused by deletions or pathogenic variants in the CREBBP gene and accounts for roughly 50-60% of RSTS cases. RSTS type 2 makes up about 8-10% of RSTS cases and is associated with pathogenic variations in the EP300 gene [43-46].

Obesity Syndromes with Chromosomal and Imprinting Anomalies

A number of additional chromosomal syndromes, particularly deletions of chromosomes, have been discovered in conjunction with obesity. Obesity is typically developed in patients who carry these syndromes, but this is not always the case. In light of this, it is possible that the development of obesity requires either penetrance or variable expression levels. The following syndromes are included, but not limited to: 11p13 (WAGR syndrome), 1p36 (monosomy 1p36 syndrome), 9q34 (Kleefstra syndrome), 17p11.2 (Smith-Magenis syndrome), 6q16 (PWS-like syndrome) and 2q37 (brachydactyly mental retardation syndrome; BDMR). In these certain genes, haploinsufficiency is likely to account for specific observed phenotypes [47]. A few of them are as follows:

Prader-Willi Syndrome (PWS)

PWS is recognized as the most prevalent genetic cause of obesity, reported in about 1 in 10,000 to 1 in 30,000 live births [48,49]. PWS is caused due to the absence of expression of genes that are derived from the father in the critical region of the PWS gene, situated on chromosome 15q11-q13. Approximately 65-70% of the observed cases are attributed to the deletion of this region (type 1 or type 2, depending on the proximal break point). 20-30% of the cases are due to a maternal uniparental disomy of chromosome 15 and the majority of the remaining two percent to five percent have an imprinting center defect or unbalanced translocations (about one percent) [50,51]. PWS is a complex multisystem disorder marked by short stature, behavioral issues, short stature, psychiatric disorders, feeding difficulties in early infancy, neonatal hypotonia, cognitive deficits and distinctive physical characteristics (prominent facial features, scoliosis, reduced hand and foot size and narrow hands with a straight ulnar border). It also involves various endocrine disorders (growth hormone [GH]/insulin-like growth factor-I axis dysfunction, hypogonadism, central adrenal insufficiency, hypothyroidism), early onset of hyperphagia with food-seeking behavior leading to severe obesity if dietary intake remains unchecked [52]. A complex dysregulation of the hypothalamus is presently believed to account for the PWS phenotype [53]. From ages 1 to 6, Mild obesity begins about 1 year of age, with hyperphagia and severe obesity often manifesting between ages 2 and 6. In the absence of suitable dietary restrictions, environmental management and behavioral interventions, obesity advances into adulthood, resulting in obesity-related health issues, including chronic leg edema, thrombophlebitis, T2DM, cardiopulmonary disease and mortality before the age of 35 [54] According to Rahman *et al.* [55], the probable causes of hyperphagia include hormonal anomalies, which involve elevated levels of leptin and ghrelin from infancy to adulthood. At certain ages, hormone levels in the thyroid, insulin and peptide YY decreased. In individuals ranging from 4 to 30 years old, neuronal abnormalities linked to Orexin A and changes in brain structure were found.

Deletion 6q16

Prior research has linked interstitial deletion of chromosome 6q16 to a PWS like phenotype, characterized by shortened extremities, hypotonia, developmental delay and obesity. In instances of obesity, recognized candidate genes have been detected within significant genomic intervals such as SIM1 (6q16) and BDNF (11p13) [56]. Children with deletions exhibit strabismus, a thin upper lip, almond-shaped eyes, hypogonadism, learning disabilities, microretrognathia, developmental delays, small hands and feet, hypotonia,

behavioral issues, cerebellar signs and neonatal feeding difficulties, presenting similarities with characteristics observed in PWS [57].

Deletion 1p36

Monosomy 1p36, also known as 1p36 deletion syndrome, is a subtelomeric monosomy occurring in 1 in every 5000 births. The primary clinical characteristics of this syndrome encompass hypotonia and motor developmental delay, accompanied by craniofacial dysmorphisms and short stature, including prominent forehead and chin, deep-set eyes, large anterior fontanel, a flat nasal bridge, ear asymmetry and maxillary hypoplasia [58,59]. It was reported in a 9 year old with generalized obesity, who had a BMI above the 95th percentile, along with acanthosis nigricans on the arms and neck. The child also had broad nasal bridge, deep-set eyes, straight eyebrows, self-inflicted lesions and a pointed chin. Cytogenetic analysis revealed a deletion at 1p36.33-pter [60]. A different investigation revealed that obesity as a result of hyperphagia was present in two patients with mosaic deletions of 1p36, suggesting that those with 1p36 deletions may be susceptible to hyperphagia and obesity when both of the subsequent risk factors; deletions that cover 2-3 Mb critical region and less severe phenotypes that lead to overeating due to independent access to food are present [61].

Deletion 2q37

Deletions of distal 2q37 area comprise of terminal cytogenetic band on the long arm of chromosome 2, separated into three sub bands: 2q37.1, 2q37.2 and 2q37.3. In previous studies, deletions have been recorded in 4,115 patients, with clinical associations to obesity, brachydactyly, short stature and intellectual deficiency, collectively termed Albright's hereditary osteodystrophy-like syndrome [62]. Their features often include deep-set eyes, sparse hair, a round face, a bulbous nasal tip and thin lip borders. Numerous individuals experience seizures alongside mild cognitive impairment, with obesity occasionally observed [63].

Deletion 9q34.3

Most patients had sub-microscopic deletions in the subtelomeric region of chromosome 9q34.3, which ranged from less than 400kb to more than 3Mb [64]. Commonly observed characteristics include early-onset obesity accompanied by hyperphagia (Occurring in 2 to 3 years of age), significant developmental delay, intellectual disability, distinctive facial features (such as synophrys, brachycephaly, prognathism, anteverted nostrils and a thin upper lip), a neonatal hypotonia, syndactyly of toes, short neck and limbs, abnormal genitalia including micropenis, hypospadias, cryptorchidism, stereotypic hand movements, abnormal sleep with recurrent nocturnal awakenings and diminished attention span [65-67].

X-Linked Obesity Syndromes

Fragile X Syndrome (FXS)

Obesity is a prevalent issue in FXS, attributed to the molecular similarities between obesity-related disorders, notably PWS [63]. FXS results from a CGG expansion exceeding 200 repeats in the 5' untranslated region of FXS mental retardation 1 (FMR1) gene [68]. Increased repetitions may lead to either a premutation (55 to 200 repeats) or a full mutation (over 200 CGG repeats) status. The methylation of the promoter region due to a full mutation can lead to minimal or absence of production of FMR1 mRNA and consequently a deficiency of the FMR1 protein [69]. A study comprising of 260 patients with FXS (198 males and 62 females) was conducted by the Fragile X Clinical and Research Consortium. It was discovered that weight of children and adolescents with FXS may exceed that of general population [70]. Raspa *et al.* [71] collected data from a national survey that included 884 families to evaluate the general health of both adults and children with FXS. Obesity prevalence among adults with FXS aligns closely with that of the general population, estimated at around 30%. Male children with FXS showed increased obesity rates (31%) in contrast to their normally developing counterparts of the same age (18%).

Börjeson-Forssman-Lehmann Syndrome (BFLS)

BFLS is a relatively rare X-linked disorder characterized by significant cognitive deficits, prominent fleshy ears, obesity with gynecomastia, hypogonadism and distinct facial morphology [72]. Individuals with BFLS generally show a normal birth weight; however, they demonstrate substantial truncal obesity by late childhood. Despite notable differences in obesity levels, individuals with reduced overall fat often display a fat distribution in the lower abdomen and hips in the same pattern as females. The Plant homeodomain finger gene 6(PHF6) has been identified as the gene that is altered in patients with BFLS [73]. The clinical history and physical examination of all affected males suggest that this phenotype exhibits a less severe yet more variable presentation than previously recorded, with changes observed with age [74].

Case Studies in Saudi Arabia

Research has shown a notable prevalence of obesity, especially in children, among the Saudi population, which demonstrates a high level of consanguinity. Consanguinity is particularly prevalent in many Arab nations, with rates ranging from 20 to 50% of all marriages [75]. Mohammed *et al.* [76]. conducted a systematic review in 2023 and explored genetic conditions leading to monogenic obesity in a cohort of 243 children from Qatar. In a study, thirty rare variants that may be associated with obesity were discovered in 36 of the 243 probands, representing 14.8%, across 15 candidate genes. Variants in the MC4R gene emerged as primary contributor to obesity, responsible for as much as 19% of cases.

Progress in genetics has enabled researchers to isolate mutations associated with the onset of BBS, namely the BBS1, BBS2, ARL6/BBS3, MKKS/BBS6, BBS7, TTC8/BBS8, B1/BBS9, BBS10 and TRIM32/BBS11 genes [77,78]. The prevalence of BBS genes mutations, particularly BBS3 and BBS9, have been observed in populations of Asian descent, such as those from Saudi Arabia and India, compared to other populations [79,80]. There exist numerous phenotypes of BBS that vary in disease severity, contingent upon the locus of the mutated gene, with most documented cases associated with mutations in different BBS genes [20]. In 2022, Alhamoud M et al. documented an instance of BBS in a five-year-old Saudi girl, who exhibited obesity subsequent to hypogonadism and polydactyly, among other symptoms. The child exhibited typical indicators of central obesity, characterized by a rounded facial appearance and dysmorphic traits. Genetic testing in the patient revealed the variant of uncertain significance c.1553-1G>A p.? likely in homozygosity within the BBS9 gene located on chromosome 7, demonstrating an autosomal recessive inheritance pattern, which supports our clinical diagnosis of BBS9 [81]. In 2024, Milibari et al. identified 46 individuals with BBS from 31 Saudi families, with obesity observed in 91% of the patients [82]. An increased prevalence of obesity among both children and adults was found in the clinical spectrum of 11 patients from four consanguineous families in Saudi Arabia in a study by Cherian and Al-Sanna'a [83].

Regional variations exist and the BBS4, BBS5 and BBS8 mutations were predominately present within patients from the Middle East specifically, North Africa, Kuwait and Saudi Arabia [83]. BBS4 had little effect on BBS, even though it is significantly more common in Arab families compared to white families in Europe and North America [21,84-88]. A concise methodology, grounded in the prevalence of pathogenic mutations, is necessary for the molecular diagnosis of BBS given its considerable heterogeneity.

A study involving 12 patients with ALMS, including 9 children, revealed genetic and medical heterogeneity; 6 of them exhibited a founder mutation (IVS18-2A>T in exon 19), while the remaining 6 exhibited private mutations [89]. Aldahmesh *et al.* [90] demonstrated that, regardless of population-level endogamy, a consanguineous union suffices to render a genomic area homozygous, directly correlating with the degree of consanguinity. Four novel alleles were identified, utilizing ALMS to demonstrate the significant phenomenon of allelic heterogeneity in a rare autosomal recessive disorder among a highly inbred Saudi population. It has been observed that with an average consanguinity rate of around 50%, individuals from Saudi Arabia are expected to have a considerably higher number of homozygosity blocks compared to many other populations. Bakar *et al.* [91] documented a case involving a 10-year-old girl from a clinic in Saudi Arabia, whose weight was positioned in the 80th percentile for her age group. Their emphasis was on the necessity for physicians to perform tests for ALMS when faced with a combination of obesity, diabetes, auditory impairment and visual impairment. Consequently, ALMS in Saudi Arabia is likely undetected due to diverse medical presentations.

Mochida *et al.* [92] investigated Cohen syndrome in four populations and discovered that afflicted individuals in the Saudi Arabian lineage were homozygous for a novel mutation, 1219 C.T, in exon 9. This mutation converts a glutamine residue at position 407 of 4022 into a termination codon (Q407X), resulting in significantly truncated predicted protein. In a separate study, Hashmi *et al.* [93] examined a consanguineous Saudi family with three affected members. No distinct characteristics such as truncal obesity and musculoskeletal deformities, including hypotonia, were observed. However, in spite of the common symptoms, a definitive diagnosis of Cohen syndrome can only be established through genetic testing. Al-Qattan *et al.* [94] documented a case of RTS Type I in a 4-year-old Saudi boy, who was identified as heterozygous for a sequence variant c.4963del in the CREBBP gene, anticipated to cause premature protein termination. The child and his father were identified as heterozygous for the EP300 gene variant and anticipated to cause the amino acid substitution.

In the Al-Baha Region of Saudi Arabia, Al Ghamdi *et al.* [95] conducted a study involving 744 children and adolescents to outline the patterns and clinical outcomes associated with various non-diabetic pediatric endocrine disorders. Obesity was reported in 123 cases, accounting for 16.5%, whereas syndromes with endocrine characteristics were identified in 14 cases, representing 1.9%, which included 2 instances of PWS. Al Herbish *et al.* [96] identified that among 52 children referred to a tertiary health center in Riyadh for childhood obesity, 3 (5.8%) were diagnosed with PWS. A case involving an 8-year-old girl from Saudi Arabia has been documented, highlighting deletions on chromosome 1 at q31 and q42.1, along with congenital glaucoma present from birth. She exhibited bilateral buphthalmos with extensive opacities in the corneas and she was incapable of following or fixating on any directional gaze with either eye. Obesity was not identified as one of the symptoms [97]. Iqbal *et al.* [98] conducted an evaluation of the prevalence of FXS-positive cases within a cohort of 305 preselected individuals. In males, the FXS-positive cells ranged from 7% to 58%, whereas in females, it ranged from 14% to 21%. Al-Hur *et al.* [99] proposed a significant impact of consanguineous marriage on the frequency of FXS in the Eastern Region of Saudi Arabia. The assessment for related diseases demonstrated a direct correlation with rising rates in male instances with FXS. However, obesity was not a confounding factor in these cases.

CONCLUSION

The obesity pandemic can be attributed significantly to lifestyle changes that have occurred over the past three decades. Genetic testing validates clinical diagnosis and Genetic counselling are of utmost importance for early diagnosis in children and assist families dealing with genetic

obesity syndromes. Nevertheless, the prevalence of childhood obesity cannot be determined solely by the obesogenic environment; it must be accompanied by genetic predisposition. Unique disease susceptibility genotypes among Arabs are also significant contributing factors to obesity. In this review, some of the obesity-associated variations were also found in other ethnic, regional groups, but complicated gene-environment interactions enhance these genotypes, predisposing them to obesity. Consequently, the absence of genetic association studies focused on obesity within Arab populations highlights the necessity for more rigorously designed research and lack of longitudinal data to elucidate the genetic framework contributing to obesity potential in this particular population. Future research should focus on Conducting longitudinal studies on obesity progression in Saudi populations, investigating the genetic-environment interaction in obesity syndromes and exploring novel genetic mutations unique to the Arab population.

REFERENCES

[1] Faienza, Maria Felicia, *et al.* "Childhood obesity, cardiovascular and liver health: a growing epidemic with age." *World Journal of Pediatrics,* vol. 16, no. 5, October 2020, pp. 438-445. https://pubmed.ncbi.nlm.nih.gov/32020441/.

[2] Mirmiran, P., *et al.* "Childhood obesity in the Middle East: a review." *Eastern Mediterranean Health Journal,* vol. 16, no. 9, September 2010, pp. 1009-1017. https://pubmed.ncbi.nlm.nih.gov/21218730/.

[3] Sharav, T. and T. Bowman. "Dietary practices, physical activity, and body-mass index in a selected population of Down syndrome children and their siblings." *Clinical Pediatrics,* vol. 31, no. 6, June 1992, pp. 341-344. https://pubmed.ncbi.nlm.nih.gov/1385771/.

[4] El-Hazmi, Mohsen A. F. and Arjumand S. Warsy. "A comparative study of prevalence of overweight and obesity in children in different provinces of Saudi Arabia." *Journal of Tropical Pediatrics,* vol. 48, no. 3, June 2002, pp. 172-177. https://pubmed.ncbi.nlm.nih.gov/12164602/.

[5] Serra-Juhé, Clara, *et al.* "Heterozygous rare genetic variants in non-syndromic early-onset obesity." *International Journal of Obesity,* vol. 44, no. 4, April 2020, pp. 830-841. https://pubmed.ncbi.nlm.nih.gov/30926952/.

[6] Stunkard, A. J., *et al.* "The body-mass index of twins who have been reared apart." *The New England Journal of Medicine,* vol. 322, no. 21, May 1990, pp. 1483-1487. https://pubmed.ncbi.nlm.nih.gov/2336075/.

[7] Hruby, Adela and Frank B. Hu. "The Epidemiology of Obesity: A Big Picture." *PharmacoEconomics,* vol. 33, no. 7, July 2015, pp. 673-689. https://pubmed.ncbi.nlm.nih.gov/25471927/.

[8] Manco, Melania and Bruno Dallapiccola. "Genetics of pediatric obesity." *Pediatrics,* vol. 130, no. 1, July 2012, pp. 123-133. https://pubmed.ncbi.nlm.nih.gov/22665408/.

[9] Haberstick, Brett C., *et al.* "Stable genes and changing environments: body mass index across adolescence and young adulthood." *Behavior Genetics,* vol. 40, no. 4, July 2010, pp. 495-504. https://pubmed.ncbi.nlm.nih.gov/20087641/.

[10] Schousboe, Karoline *et al.* "Sex differences in heritability of BMI: a comparative study of results from twin studies in eight countries." *Twin Research,* vol. 6, no. 5, October 2003, pp. 409-421. https://pubmed.ncbi.nlm.nih.gov/14624725/.

[11] Brune, Bettina C. *et al.* "Early Postnatal BMI Adaptation Is Regulated During a Fixed Time Period and Mainly Depends on Maternal BMI." *Obesity,* vol. 18, no. 4, September 2012, pp. 798-802. https://onlinelibrary.wiley.com/doi/10.1038/oby.2009.342.

[12] Freedman, D.S. *et al.* "The relation of overweight to cardiovascular risk factors among children and adolescents: the Bogalusa Heart Study." *Pediatrics,* vol. 103, no. 6 Pt 1, June 1999, pp. 1175-1182. https://pubmed.ncbi.nlm.nih.gov/10353925/.

[13] Freedman, David S. *et al.* "The relation of childhood BMI to adult adiposity: the Bogalusa Heart Study." *Pediatrics,* vol. 115, no. 1, January 2005, pp. 22-27. https://pubmed.ncbi.nlm.nih.gov/15629977/.

[14] Kelishadi, Roya. "Childhood overweight, obesity, and the metabolic syndrome in developing countries." *Epidemiologic Reviews,* vol. 29, 2007, pp. 62-76. https://pubmed.ncbi.nlm.nih.gov/17478440/.

[15] Younes, Salma*et al.* "Genetic polymorphisms associated with obesity in the Arab world: a systematic review." *International Journal of Obesity,* vol. 45, no. 9, September 2021, pp. 1899-1913. https://pubmed.ncbi.nlm.nih.gov/34131278/.

[16] AbouHashem, Nadien *et al.* "The genetic elucidation of monogenic obesity in the Arab world: a systematic review." *Journal of Pediatric Endocrinology & Metabolism,* vol. 35, no. 6, April 2022, pp. 699-707. https://pubmed.ncbi.nlm.nih.gov/35437977/.

[17] Cummings, David E. and Michael W. Schwartz. "Genetics and pathophysiology of human obesity." *Annual Review of Medicine,* vol. 54, 2003, pp. 453-471. https://pubmed.ncbi.nlm.nih.gov/12414915/.

[18] Farooqi, Sadaf and Stephen O'Rahilly. "Monogenic obesity in humans." *Annual Review of Medicine,* vol. 56, 2005, pp. 443-458. https://pubmed.ncbi.nlm.nih.gov/15660521/.

[19] Kaur, Y. *et al.* "A systematic review of genetic syndromes with obesity." *Obesity Reviews,* vol. 18, no. 6, June 2017, pp. 603-634. https://pubmed.ncbi.nlm.nih.gov/28346723/.

[20] Khan, S.A. *et al.* "Genetics of human Bardet-Biedl syndrome, an updates." *Clinical Genetics,* vol. 90, no. 1, July 2016, pp. 3-15. https://pubmed.ncbi.nlm.nih.gov/26762677/.

[21] Forsythe, Elizabeth and Philip L. Beales. "Bardet-Biedl syndrome." *European Journal of Human Genetics,* vol. 21, no. 1, January 2013, pp. 8-13. https://pubmed.ncbi.nlm.nih.gov/22713813/.

[22] Moore, Susan J. *et al.* "Clinical and genetic epidemiology of Bardet-Biedl syndrome in Newfoundland: A 22-year prospective, population-based, cohort study." *American Journal of Medical Genetics,* vol. 132A, no. 4, February 2005, pp. 352-360. https://pubmed.ncbi.nlm.nih.gov/15637713/.

[23] Davis, Roger E. *et al.* "A knockin mouse model of the Bardet-Biedl syndrome 1 M390R mutation has cilia defects, ventriculomegaly, retinopathy, and obesity." *Proceedings of the National Academy of Sciences of the United States of America,* vol. 104, no. 49, December 2007, pp. 19422-19427. https://pubmed.ncbi.nlm.nih.gov/18032602/.

[24] Wellen, Kathryn E. and Gökhan S. Hotamisligil. "Inflammation, stress, and diabetes." *The Journal of Clinical Investigation,* vol. 115, no. 5, May 2005, pp. 1111-1119. https://pubmed.ncbi.nlm.nih.gov/15864338/.

[25] Dassie, Francesca *et al.* "Alström syndrome: an ultra-rare monogenic disorder as a model for insulin resistance, type 2 diabetes mellitus and obesity." *Endocrine,* vol. 71, no. 3, March 2021, pp. 618-625. https://pubmed.ncbi.nlm.nih.gov/33566311/.

[26] Álvarez-Satta, María *et al.* "Alström syndrome: current perspectives." *The Application of Clinical Genetics,* vol. 8, July 2015, pp. 171-179. https://pubmed.ncbi.nlm.nih.gov/26229500/.

[27] Abosabie, Salma A.S. *et al.* "Unraveling Alström syndrome: Homozygous mutation c.2729C>G in ALMS1 gene across an extended family." *Molecular Genetics & Genomic Medicine,* vol. 12, no. 1, January 2024. https://pubmed.ncbi.nlm.nih.gov/37937857/.

[28] Wang, Heng *et al. Cohen Syndrome* GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle 2006, https://pubmed.ncbi.nlm.nih.gov/20301655/. https://pubmed.ncbi.nlm.nih.gov/20301655/.

[29] Becerra, Nancy Mora and Dina Block. "Cohen Syndrome as Cause of Childhood Central Obesity Leading to Increased Risk of Metabolic Complications." *Proceedings of UCLA Health,* vol. 21, no. 1, July 2017. https://escholarship.org/uc/item/6qh5q102.

[30] Gunay-Aygun, M. *et al.* "Prader-Willi and other syndromes associated with obesity and mental retardation." *Behavior Genetics,* vol. 27, no. 4, July 1997, pp. 307-324. https://pubmed.ncbi.nlm.nih.gov/9519559/.

[31] Cohen, D.M. *et al.* "Acrocephalopolysyndactyly type II--Carpenter syndrome: clinical spectrum and an attempt at unification with Goodman and Summit syndromes." *American Journal of Medical Genetics,* vol. 28, no. 2, October 1987, pp. 311-324. https://pubmed.ncbi.nlm.nih.gov/3322002/.

[32] Bouaré, Fah *et al.* "Complex craniosynostosis in the context of Carpenter's syndrome." *Child's nervous system,* vol. 38, no. 4, April 2022, pp. 831-835. https://pubmed.ncbi.nlm.nih.gov/34244844/..

[33] Hidestrand, Pip *et al.* "Carpenter syndrome." *The Journal of Craniofacial Surgery,* vol. 20, no. 1, January 2009, pp. 254-256. https://pubmed.ncbi.nlm.nih.gov/19165041/.

[34] Jenkins, Dagan *et al.* "RAB23 mutations in Carpenter syndrome imply an unexpected role for hedgehog signaling in cranial-suture development and obesity." *American Journal of Human Genetics,* vol. 80, no. 6, June 2007, pp. 1162-1170. https://pubmed.ncbi.nlm.nih.gov/17503333/.

[35] Khairat, Rabab *et al.* "Expansion of the phenotypic and mutational spectrum of Carpenter syndrome." *European Journal of Medical Genetics,* vol. 65, no. 1, January 2022. https://pubmed.ncbi.nlm.nih.gov/34748996/.

[36] Twigg, Stephen R.F. *et al.* "Mutations in multidomain protein MEGF8 identify a Carpenter syndrome subtype associated with defective lateralization." *American Journal of Human Genetics,* vol. 91, no. 5, November 2012, pp. 897-905. https://pubmed.ncbi.nlm.nih.gov/23063620/.

[37] Albright, F.B.C.H. "Pseudohypoparathyroidism: an example of" Seabright-Bantam syndrome." *Endocrinology,* vol. 30, 1942, pp. 922-932. https://cir.nii.ac.jp/crid/1572261549991718912.

[38] Weinstein, L.S. *et al.* "Endocrine manifestations of stimulatory G protein alpha-subunit mutations and the role of genomic imprinting." *Endocrine Society,* vol. 22, no. 5, October 2001, pp. 675-705. https://pubmed.ncbi.nlm.nih.gov/11588148/.

[39] Ong, K.K. *et al.* "Pseudohypoparathyroidism--another monogenic obesity syndrome." *Clinical Endocrinology,* vol. 52, no. 3, March 2000, pp. 389-391. https://pubmed.ncbi.nlm.nih.gov/10718839/.

[40] Lacombe, Didier *et al.* "Diagnosis and management in Rubinstein-Taybi syndrome: first international consensus statement." *Journal of Medical Genetics,* vol. 61, no. 6, May 2024, pp. 503-519. https://pubmed.ncbi.nlm.nih.gov/38471765/.

[41] Douzgou, Sofia *et al.* "The natural history of adults with Rubinstein-Taybi syndrome: a families-reported experience." *European Journal of Human Genetics,* vol. 30, no. 7, July 2022, pp. 841-847. https://pubmed.ncbi.nlm.nih.gov/35388185/.

[42] Spena, S. *et al.* "Insights into genotype-phenotype correlations from CREBBP point mutation screening in a cohort of 46 Rubinstein-Taybi syndrome patients." *Clinical Genetics,* vol. 88, no. 5, November 2015, pp. 431-440. https://pubmed.ncbi.nlm.nih.gov/25388907/.

[43] Fergelot, Patricia *et al.* "Phenotype and genotype in 52 patients with Rubinstein-Taybi syndrome caused by EP300 mutations." *American Journal of Medical Genetics,* vol. 170, no. 12, December 2016, pp. 3069-3082. https://pubmed.ncbi.nlm.nih.gov/27648933/.'

[44] Stevens, Cathy A. *et al.* "Adults with Rubinstein-Taybi syndrome." *American Journal of Medical Genetics,* vol. 155A, no. 7, July 2011, pp. 1680-1684. https://pubmed.ncbi.nlm.nih.gov/21671385/.

[45] Roelfsema, Jeroen H. *et al.* "Genetic heterogeneity in Rubinstein-Taybi syndrome: mutations in both the CBP and EP300 genes cause disease." *American Journal of Human Genetics,* vol. 76, no. 4, April 2005, pp. 572-580. https://pubmed.ncbi.nlm.nih.gov/15706485/.

[46] Negri, G. *et al.* "Clinical and molecular characterization of Rubinstein-Taybi syndrome patients carrying distinct novel mutations of the EP300 gene." *Clinical Genetics,* vol. 87, no. 2, February 2015, pp. 148-154. https://pubmed.ncbi.nlm.nih.gov/24476420/.

[47] D'Angelo, Carla Sustek and Celia Priszkulnik Koiffmann. "Copy number variants in obesity-related syndromes: review and perspectives on novel molecular approaches." *Journal of Obesity,* vol. 2012, December 2012. https://pubmed.ncbi.nlm.nih.gov/23316347/.

[48] Cassidy, Suzanne B. *et al.* "Prader-Willi syndrome." *Genetics in Medicine,* vol. 14, no. 1, January 2012, pp. 10-26. https://pubmed.ncbi.nlm.nih.gov/22237428/.

[49] Lionti, Tess *et al.* "A population-based profile of 160 Australians with Prader-Willi syndrome: trends in diagnosis, birth prevalence and birth characteristics." *American Journal of Medical Genetics,* vol. 167A, no. 2, February 2015, pp. 371-378. https://pubmed.ncbi.nlm.nih.gov/25424396/.

[50] Butler, Merlin G. *et al.* "Prader-Willi Syndrome: Clinical Genetics and Diagnostic Aspects with Treatment Approaches." *Current Pediatric reviews,* vol. 12, no. 2, February 2015, pp. 136-166. https://pubmed.ncbi.nlm.nih.gov/26592417/.

[51] Angulo, M.A. *et al.* "Prader-Willi syndrome: a review of clinical, genetic, and endocrine findings." *Journal of Endocrinological Investigation,* vol. 38, no. 12, December 2015, pp. 1249-12263. https://pubmed.ncbi.nlm.nih.gov/26062517/.

[52] Heksch, Ryan *et al.* "Review of Prader-Willi syndrome: the endocrine approach." *Translational Pediatrics,* vol. 6, no. 4, October 2017, pp. 274-285. https://pubmed.ncbi.nlm.nih.gov/29184809/.

[53] Crinò, Antonino *et al.* "Obesity management in Prader-Willi syndrome: current perspectives." *Diabetes, Metabolic Syndrome and Obesity,* vol. 4, no. 11, October 2018, pp. 579-593. https://pubmed.ncbi.nlm.nih.gov/30323638/.

[54] Goldstone, Anthony P. and Philip L. Beales. "Genetic obesity syndromes." *Frontiers of Hormone Research,* vol. 36, 2008, pp. 37-60. https://pubmed.ncbi.nlm.nih.gov/18230893/.

[55] Rahman, Qaddra Fahada Ab *et al.* "Hyperphagia in Prader-Willi syndrome with obesity: From development to pharmacological treatment." *Intractable & Rare Diseases Research,* vol. 12, no. 1, February 2023, pp. 5-12. https://pubmed.ncbi.nlm.nih.gov/36873672/.

[56] Bonaglia, Maria Clara *et al.* "Detailed phenotype-genotype study in five patients with chromosome 6q16 deletion: narrowing the critical region for Prader-Willi-like phenotype." *European Journal of Human Genetics,* vol. 16, no. 12, December 2008, pp. 1443-1449. https://pubmed.ncbi.nlm.nih.gov/18648397/.

[57] Wentzel, C. *et al.* "Interstitial Deletions at 6q14.1-q15 Associated with Obesity, Developmental Delay and a Distinct Clinical Phenotype." *Molecular Syndromology,* vol. 1, no. 2, December 2008, pp. 75-81. https://pubmed.ncbi.nlm.nih.gov/21045960/.

[58] Seo, Go Hun *et al.* "Identification of 1p36 deletion syndrome in patients with facial dysmorphism and developmental delay." *Korean journal of Pediatrics,* vol. 59, no. 1, January 2016, pp. 16-23. https://pubmed.ncbi.nlm.nih.gov/26893599/.

[59] Shiba, Naoko *et al.* "Neuropathology of brain and spinal malformations in a case of monosomy 1p36." *Acta Neuropathologica Communications,* vol. 1, no. 1, August 2013. https://actaneurocomms.biomedcentral.com/articles/10.1186/2051-5960-1-45.

[60] Zagalo, Ana *et al.* "Morbid obesity in a child with monosomy 1p36 syndrome." *BMJ Case Reports,* vol. 2012, March 2012. https://pubmed.ncbi.nlm.nih.gov/22605691/.

[61] Shimada, Shino *et al.* "Mild developmental delay and obesity in two patients with mosaic 1p36 deletion syndrome." *American Journal of Medical Genetics,* vol. 164, no. 2, December 2013, pp. 415-420. https://onlinelibrary.wiley.com/doi/10.1002/ajmg.a.36304.

[62] Chen, Chih Ping *et al.* "Deletion 2q37. 3 [arrow right] qter and duplication 15q24. 3 [arrow right] qter characterized by array cgh in a girl with epilepsy and dysmorphic features." *Genetic Counseling,* vol. 21, no. 2, 2010. https://www.proquest.com/openview/0177aa23e8faad638a041d60bb31f194/1?cbl=36889&pq-origsite=gscholar.

[63] Leroy, Camille *et al.* "The 2q37-deletion syndrome: an update of the clinical spectrum including overweight, brachydactyly and behavioural features in 14 new patients." *European Journal of Human Genetics,* vol. 21, no. 6, June 2013, pp. 602-612. https://pubmed.ncbi.nlm.nih.gov/23073310/.

[64] Stewart, Douglas R. and Tjitske Kleefstra. "The chromosome 9q subtelomere deletion syndrome." *American Journal of Medical Genetics,* vol. 145C, no. 4, November 2007, pp. 383-392. https://pubmed.ncbi.nlm.nih.gov/17910072/.

[65] Cormier-Daire, V. *et al.* "Cryptic terminal deletion of chromosome 9q34: a novel cause of syndromic obesity in childhood?." *Journal of Medical Genetics,* vol. 40, no. 4, April 2003, pp. 300-303. https://pmc.ncbi.nlm.nih.gov/articles/PMC1735435/.

[66] Iwakoshi, Mie *et al.* "9q34.3 deletion syndrome in three unrelated children." *American Journal of Medical Genetics,* vol. 126A, no. 3, April 2004, pp. 278-283. https://pubmed.ncbi.nlm.nih.gov/15054842/.

[67] Nowicki, Stephen T. *et al.* "The Prader-Willi phenotype of fragile X syndrome." *Journal of Developmental and Behavioral Pediatrics,* vol. 28, no. 2, April 2007, pp. 133-138. https://pubmed.ncbi.nlm.nih.gov/17435464/.

[68] McLennan, Yingratana *et al.* "Fragile x syndrome." *Current Genomics,* vol. 12, no. 3, May 2011, pp. 216-224. https://pubmed.ncbi.nlm.nih.gov/22043169/.

[69] Zang, Julie B. *et al.* "A mouse model of the human Fragile X syndrome I304N mutation." *Public Library of Science Genetics,* vol. 5, no. 12, December 2009. https://pubmed.ncbi.nlm.nih.gov/20011099/.

[70] Kidd, Sharon A. *et al.* "Fragile X syndrome: a review of associated medical problems." *Pediatrics,* vol. 134, no. 5, November 2014, pp. 995-1005. https://pubmed.ncbi.nlm.nih.gov/25287458/.

[71] Raspa, Melissa *et al.* "Obesity, food selectivity, and physical activity in individuals with fragile X syndrome." *American Journal on Intellectual and Developmental Disabilities,* vol. 115, no. 6, November 2010, pp. 482-495. https://pubmed.ncbi.nlm.nih.gov/20946001/.

[72] Borjesonm, M. *et al.* "An X-linked, recessively inherited syndrome characterized by grave mental deficiency, epilepsy, and endocrine disorder." *Acta Medica Scandinavica,* vol. 171, January 1962, pp. 13-21. https://pubmed.ncbi.nlm.nih.gov/13871358/.

[73] Voss, Anne K. *et al.* "Protein and gene expression analysis of Phf6, the gene mutated in the Börjeson–Forssman–Lehmann Syndrome of intellectual disability and obesity." *Gene Expression Patterns,* vol. 7, no. 8, January 1962, pp. 858-871. https://www.semanticscholar.org/paper/Protein-and-gene-expression-analysis-of-Phf6%2C-the-Voss-Gamble/612d955efaf7f80739db58192adbed17f8cc41a1.

[74] Turner, G. *et al.* "The clinical picture of the Börjeson-Forssman-Lehmann syndrome in males and heterozygous females with *PHF6* mutations." *Clinical Genetics,* vol. 65, no. 3, January 2004, pp. 226-232. https://onlinelibrary.wiley.com/doi/abs/10.1111/j.0009-9163.2004.00215.x.

[75] Khayat, Abdullah M. *et al.* "Consanguineous Marriage and Its Association With Genetic Disorders in Saudi Arabia: A Review." *Cureus,* vol. 16, no. 2, February 2024. https://pubmed.ncbi.nlm.nih.gov/38465157/.

[76] Mohammed, Idris *et al.* "Understanding the Genetics of Early-Onset Obesity in a Cohort of Children From Qatar." *The Journal of Clinical Endocrinology and Metabolism,* vol. 108, no. 12, November 2023, pp. 3201-3213. https://pubmed.ncbi.nlm.nih.gov/37329217/.

[77] Khan, Pathan Amanulla *et al.* "Laurence Moon Bardet Biedl Syndrome: a rare case report in a tertiary care teaching hospital, Hyderabad, Telangana, India." *International Journal of Medicine and Public Health,* vol. 7, no. 1, March 2017, pp. 68-71.

[78] Khan, Bilal Ahmed *et al.* "Laurence-Moon-Bardet-Biedl syndrome: a case report." *Cureus,* vol. 11, no. 9, 2019. https://assets.cureus.com/uploads/case_report/pdf/19663/1612428790-1612428784-20210204-18204-14787iz.pdf.

[79] Safieh, L. Abu *et al.* "Clinical and molecular characterisation of Bardet-Biedl syndrome in consanguineous populations: the power of homozygosity mapping." *Journal of Medical Genetics,* vol. 47, no. 4, April 2010, pp. 236-341. https://pubmed.ncbi.nlm.nih.gov/19858128/.

[80] Sathya Priya, C. *et al.* "Mutation spectrum in BBS genes guided by homozygosity mapping in an Indian cohort." *Clinical Genetics,* vol. 87, no. 2, January 2014, pp. 161-166. https://onlinelibrary.wiley.com/doi/abs/10.1111/cge.12342.

[81] Alhamoud, Mustafa *et al.* "Bardet-Biedl Syndrome: A Rare Case From Ophthalmology Perspective." *Cureus,* vol. 14, no. 10, October 2022. https://pubmed.ncbi.nlm.nih.gov/36348931/.

[82] Milibari, Doaa *et al.* "The Clinical and Mutational Spectrum of Bardet-Biedl Syndrome in Saudi Arabia." *Genes (Basel),* vol. 15, no. 6, June 2024. https://pubmed.ncbi.nlm.nih.gov/38927698/.

[83] Cherian, Mathew Punnachalil and Nouriya A. Al-Sanna'a. "Clinical spectrum of Bardet-Biedl syndrome among four Saudi Arabian families." *Clinical Dysmorphology,* vol. 18, no. 4, October 2009, pp. 188-194. https://pubmed.ncbi.nlm.nih.gov/19707123/.

[84] Elbedour, K. *et al.* "Cardiac abnormalities in the Bardet-Biedl syndrome: echocardiographic studies of 22 patients." *American Journal of Medical Genetics,* vol. 52, no. 2, August 1994, pp. 164-169. https://pubmed.ncbi.nlm.nih.gov/7802002/.

[85] Ajmal, Muhammad *et al.* "Exome sequencing identifies a novel and a recurrent BBS1 mutation in Pakistani families with Bardet-Biedl syndrome." *Molecular Vision,* vol. 19, 2013, pp. 644-653. https://pubmed.ncbi.nlm.nih.gov/23559858/.

[86] Khan, Saadullah *et al.* "Novel homozygous mutations in the genes ARL6 and BBS10 underlying Bardet-Biedl syndrome." *Gene,* vol. 515, no. 1, February 2013, pp. 84-88. https://pubmed.ncbi.nlm.nih.gov/23219996/.

[87] Pawlik, B. *et al.* "A Novel Familial BBS12 Mutation Associated with a Mild Phenotype: Implications for Clinical and Molecular Diagnostic Strategies." *Molecular Syndromology* vol. 1, no. 1, February 2010, pp. 27-34. https://pubmed.ncbi.nlm.nih.gov/20648243/.

[88] Katsanis, Nicholas *et al.* "BBS4 is a minor contributor to Bardet-Biedl syndrome and may also participate in triallelic inheritance." *American Journal of Human Genetics,* vol. 71, no. 1, July 2002, pp. 22-29. https://pubmed.ncbi.nlm.nih.gov/12016587/.

[89] Ghadah, Gosadi *et al.* "Alstrom's Syndrome: An Experience of Tertiary Care Center." *Journal of Pediatric Genetics,* vol. 13, no. 2, 2024, pp. 133-138. https://www.thieme-connect.com/products/ejournals/abstract/10.1055/s-0041-1740369.

[90] Aldahmesh, Mohamed A. *et al.* "Allelic heterogeneity in inbred populations: the Saudi experience with Alström syndrome as an illustrative example." *American Journal of Medical Genetics,* vol. 149, no. 4, April 2009, pp. 662-665. https://onlinelibrary.wiley.com/doi/abs/10.1002/ajmg.a.32753.

[91] Bakar, Ayman A. *et al.* "Alström syndrome: a novel mutation in Saudi girl with insulin-resistant diabetes." *Medicine,* vol. 96, no. 10, March 2017. https://journals.lww.com/md-journal/fulltext/2017/03100/Alstr_m_syndrome__A_novel_mutation_in_Saudi_girl.18.aspx.

[92] Mochida, G.H. *et al.* "Broader geographical spectrum of Cohen syndrome due to COH1 mutations." *Journal of Medical Genetics,* vol. 41, no. 6, March 2017. https://jmg.bmj.com/content/41/6/e87.short.

[93] Hashmi, Jamil A. *et al.* "Homozygosity mapping and whole exome sequencing provide exact diagnosis of Cohen syndrome in a Saudi family." *Brain & Development,* vol. 42, no. 8, September 2020, pp. 587-593. https://pubmed.ncbi.nlm.nih.gov/32402540/.

[94] Al-Qattan, Mohammad M. *et al.* "Rubinstein-Taybi syndrome in a Saudi boy with distinct features and variants in both the CREBBP and EP300 genes: a case report." *BMC Medical Genetics,* vol. 20, no. 1, January 2019. https://pubmed.ncbi.nlm.nih.gov/30635043/.

[95] Al-Ghamdi, Ahmed Hassan *et al.* "The pattern and clinical outcomes of non-diabetic pediatric endocrine disorders, Al-Baha, Saudi Arabia: a retrospective study." *Egyptian Pediatric Association Gazette,* vol. 71, no. 1, October 2023. https://link.springer.com/article/10.1186/s43054-023-00206-6.

[96] Al Herbish, Abdullah S. *et al.* "Childhood obesity: referred cases to a tertiary health center in Riyadh, Saudi Arabia." *Saudi Journal of Gastroenterology,* vol. 5, no. 2, August 1999, pp. 85-88. https://journals.lww.com/sjga/fulltext/1999/05020/Childhood_obesity__Referred_cases_to_a_tertiary.9.aspx.

[97] AlSaad, Rakan *et al.* "Chromosome 1q terminal deletion and congenital glaucoma: a case report." *The American Journal of Case Reports,* vol. 21, January 2020. https://pmc.ncbi.nlm.nih.gov/articles/PMC6977633/.

[98] Iqbal, M.A. *et al.* "Cytogenetic diagnosis of fragile X syndrome: study of 305 suspected cases in Saudi Arabia." *Annals of Saudi medicine,* vol. 20, July 2000, pp. 214-217. https://pubmed.ncbi.nlm.nih.gov/17322660/.

[99] Al-Hur, Norah Fahad and Entissar Alsuhaibani. "Consanguinity and Associated Conditions Prevalence in Fragile X Syndrome Cases in Eastern Region in Saudi Arabia." *Journal of Health, Medicine and Nursing,* vol. 36, 2017. https://www.iiste.org/Journals/index.php/JHMN/article/view/36133/37306.